# Synthetic antimicrobial agents

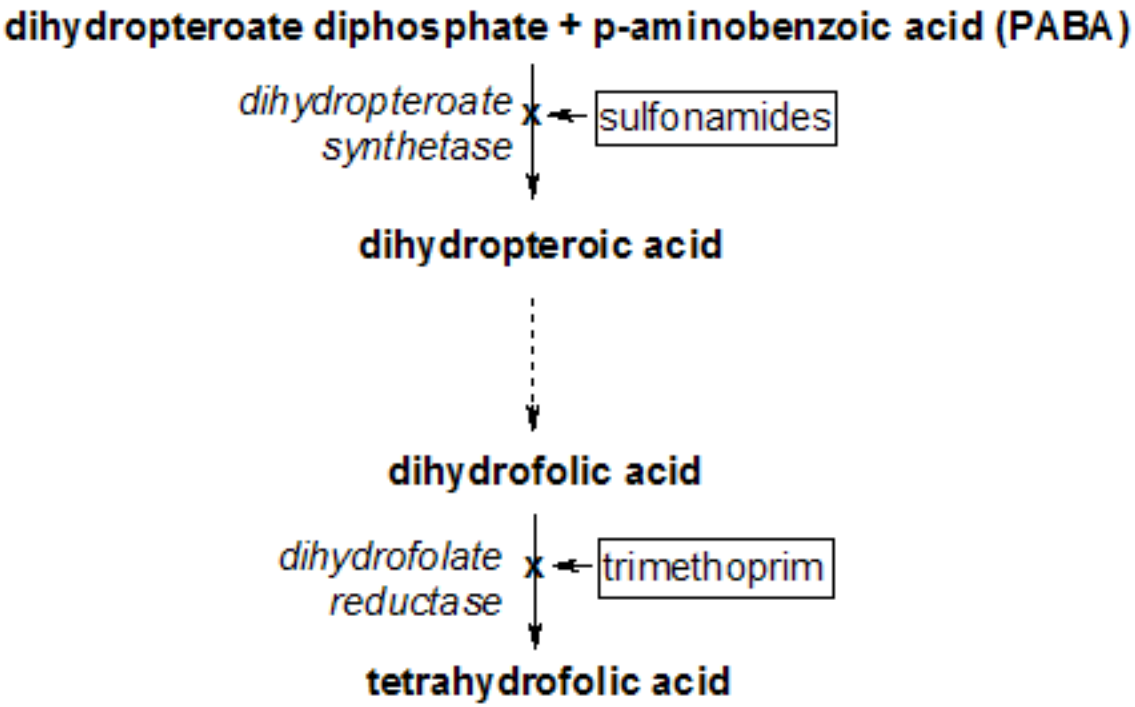
General Medicine Department for
English speaking medium

# Classification of synthetic antimicrobial agents

- ***Sulfonamides and trimethoprim***
- ***Quinolones (nalidixic acid and fluoroquinilones)***
- ***Nitrofuran derivatives***
- ***8-oxyquinoline (8-hydroxyquinoline) derivatives***
- ***Quinoxaline derivatives (dioxidine, quinoxidine, dioxicol)***
- ***Oxazolidinones***

# Sulfonamides

**The sulfonamides are synthetic bacteriostatic antimicrobials that competitively inhibit conversion of *p*-aminobenzoic acid to dihydropteroate, which bacteria need for folic acid synthesis and ultimately purine and DNA synthesis.**



# Sulfonamides

| | | |
|---|---|---|
| **Sulfonamides** | **Short-acting** | Sulfadimidine (Sulfadimizine) • Sulfamethizole **(*is available but not in Russia*)** • Sulfanilamide **(*is available as a vaginal preparation but not in Russia*)** • **Sulfapyridine • Sulfafurazole • Sulfathiazole • Sulfathiourea** |
| | **Intermediate -acting** | Sulfamethoxazole **(*in combination with* *trimethoprim* *in Russia*)** • Sulfadiazine **(*Silver sulfadiazine are available as topical preparations*) • Sulfamoxole** |
| | **Long-acting** | **Sulfadimethoxine • Sulfalene • Sulfametomidine • Sulfametoxydiazine • Sulfamethoxypyridazine • Sulfaperin • Sulfamerazine • Sulfaphenazole • Sulfamazon** |
| **Combinations** | | "Bactrim", "Co-trimaxazole" (Sulfamethoxazole plus trimethoprim) • Sulfadoxine plus pyrimethamine **(*is available but not in Russia for malaria due to chloroquine-resistant Plasmodium falciparum*)** |
| **Other** | | Sulfacetamide **(*is available as ophthalmic preparations*)** • Mafenide **(*is available as topical preparations but not in Russia*)** • Sulfisoxazole **(*is available but not in Russia*) • Prontosil • Sulfasalazine** |

# Sulfonamides: Indications

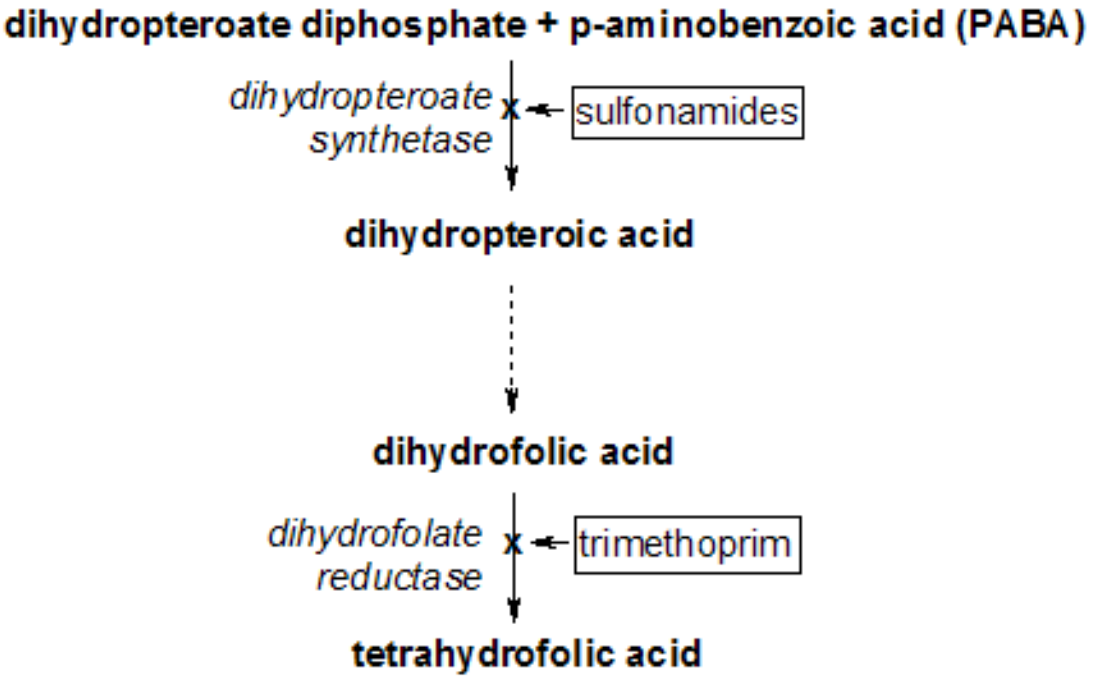
- Sulfonamides have a wide spectrum against gram-positive and many gram-negative bacteria and Plasmodium and Toxoplasma. However, resistance is widespread, and resistance to one sulfonamide indicates resistance to all.
- Sulfasalazine can be used orally for inflammatory bowel disease. Sulfonamides are most commonly used with other drugs, eg, in nocardiosis, UTI, and chloroquine-resistant *P. falciparum* malaria.
- Several sulfonamides are available for topical use: silver sulfadiazine for burns, vaginal cream and suppositories with sulfanilamide for vaginitis, and ophthalmic sulfacetamide for superficial ocular infections.

# Sulfonamides: Adverse effects

- Adverse effects can result from oral and sometimes topical sulfonamides; effects include hypersensitivity reactions; crystalluria, oliguria, and anuria; gastroenteritis; hematologic reactions, such as agranulocytosis, thrombocytopenia; photosensitivity; and neurologic effects, such as peripheral neuritis, insomnia, and headache. Pregnant women near term and neonates should not be given sulfonamides.

# Co-trimaxazole: Trimethoprim and Sulfamethoxazole

Trimethoprim is available as a single agent or combined with sulfamethoxazole; trimethoprim-sulfamethoxazole (TMP-SMX) is a fixed combination of the 2 drugs consisting of a 1:5 ratio (80 mg TMP plus 400 mg SMX or a double-strength tablet of 160 mg TMP plus 800 mg SMX).




The drugs act synergistically to block sequential steps in bacterial folic acid metabolism. TMP prevents reduction of dihydrofolate to tetrahydrofolate, and SMX inhibits conversion of *p*-aminobenzoic acid to dihydropteroate. This synergy gives maximal antibacterial activity, which is often bactericidal.

# Co-trimaxazole: Pharmacology, indication and Adverse effects

- Both drugs are well absorbed orally and are excreted in the urine. They have a serum half-life of about 11 h in plasma and penetrate well into tissues and body fluids, including the CSF. TMP is concentrated in prostatic tissue.

- TMP and TMP-SMX are active against a broad spectrum of gram-positive organisms (including some methicillin-resistant Staphylococcus aureus) and gram-negative organisms but are inactive against anaerobes, Treponema pallidum , Mycobacterium tuberculosis , Mycoplasma, and Pseudomonas aeruginosa. Enterococci and many Enterobacteriaceae and Streptococcus pneumoniae are resistant. TMP/SMX is not clinically effective for group A streptococcal pharyngitis.

- Most adverse reactions are the same as for sulfonamides. TMP causes identical adverse reactions to SMX but less commonly. When it does, nausea, vomiting, and rash occur most often. Folate deficiency (resulting in macrocytic anemia) can also occur.

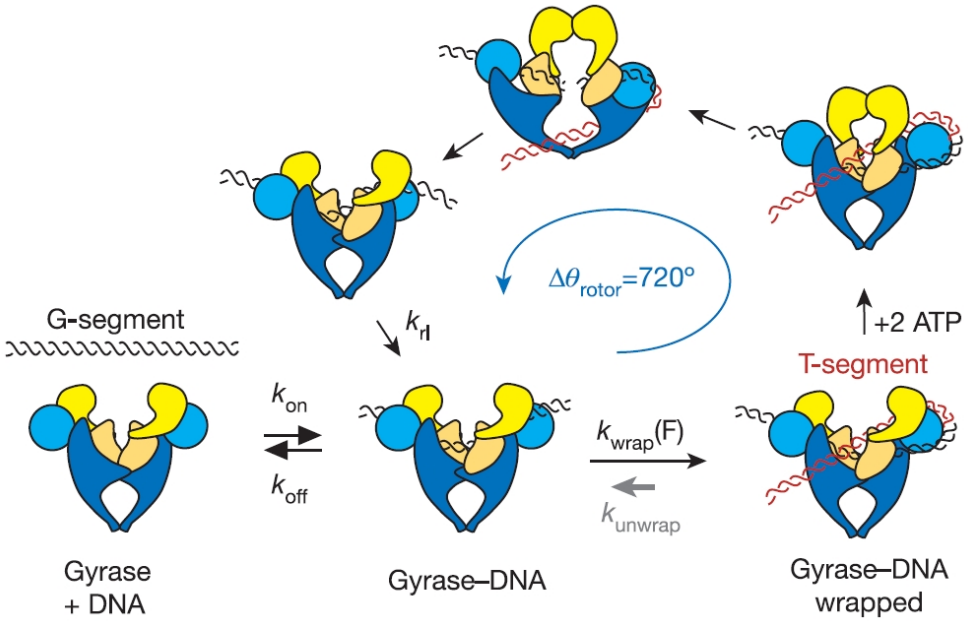
# Classification of Quinolones

| | |
|---|---|
| 1st generation<br>▫ nalidixic acid<br>▫ oxolinic acid<br>▫ pipemidic acid | |
| 2nd generation<br>▫ ciprofloxacin (Ciprobay, Cipro)<br>▫ lomefloxacin<br>▫ norfloxacin<br>▫ ofloxacin (Tarivid)<br>▫ pefloxacin | |
| 3rd generation<br>▫ levofloxacin<br>▫ sparfloxacin | |
| 4th generation<br>▫ clinafloxacin<br>▫ moxifloxacin<br>▫ gemifloxacin | |

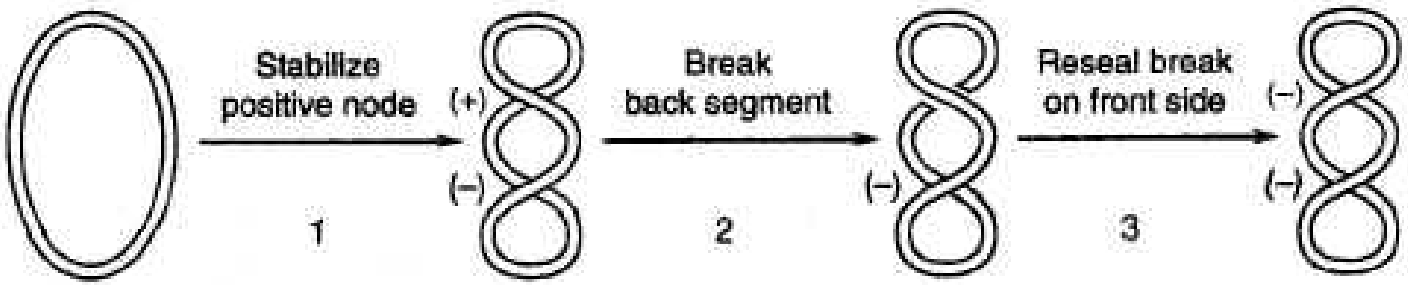
# Mechanism of Action

Dual Mechanism of Action:

1. Inhibition of bacterial DNA Gyrase (Topoisomerase II)
   - Formation of quinolone-DNA-Gyrase complex
   - Induced cleavage of DNA
2. Inhibition of bacterial Topoisomerase IV
   - Mechanism poorly understood




Mechanism of DNA Gyrase



# Adverse Effects of Quinolones

- Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain
- CNS: headache, dizziness, drowsiness, confusion, insomnia, fatigue, malaise, depression, somnolence, seizures, malaise, lightheadedness, restlessness, tremor
- Dermatologic: rash, photosensitivity reactions, pruritus
- Other: QTc prolongation, hepatotoxicity, abnormal or bitter taste, tendon rupture

# 8-oxyquinoline (8-hydroxyquinoline) derivatives

**Nitroxoline** (8-Hydroxy-5-nitroquinoline, **5-NOK**) is currently available agent in this class.

*Usage*

- Nitroxoline is a urinary antibacterial agent active against susceptible gram-positive and gram-negative organisms commonly found in urinary tract infections. Following oral administration peak plasma concentrations are achieved in 2-3 hours and maximum urinary concentrations in 4-5 hours. Nitroxoline is indicated as a secondary agent in the treatment of acute and chronic uncomplicated lower urinary tract infection.

*Adverse effects*

- Gastrointestinal disturbances can occur. These can be minimised by administration after meals. The urine of patients taking Nitroxoline is coloured yellow and readily stains skin and clothing.

# Nitrofuran derivatives

**Nitrofurantoin** and **Furazolidone** are currently available agents in this class.

*Usage*

- **Nitrofurantoin (furadonin)** is used in the treatment of initial or recurrent UTIs caused by susceptible gram-positive bacteria including enterococci and Staphylococcus aureus and gram-negative bacteria including Escherichia coli and some strains of Klebsiella, Enterobacter, and Proteus.
- **Furazolidone** is indicated as a secondary agent in the treatment of cholera caused by *Vibrio cholerae*, bacterial diarrhea caused by susceptible organisms. However, clinical studies on the effectiveness of furazolidone in some types of bacterial diarrhea have been inconclusive or conflicting. Furazolidone is indicated as a secondary agent in the treatment of giardiasis caused by Giardia lamblia.

# Nitrofurantoin (furadonin)

*Mechanism of Action*

At the concentrations achieved in urine, nitrofurantoin is bacteriocidal.

The mechanism of action: the drug works by damaging bacterial DNA, since its reduced form is highly reactive. This is made possible by the rapid reduction of nitrofurantoin inside the bacterial cell by flavoproteins (nitrofuran reductase) to multiple reactive intermediates that attack ribosomal proteins, DNA, respiration, pyruvate metabolism and other macromolecules within the cell. It is not known which of the actions of nitrofurantoin is primarily responsible for its bacteriocidal acitivity.

*Adverse effects*

- Nitrofurantoin can cause nausea and vomiting, allergic reactions, involving the skin and the bone marrow (e.g. leukopenia) and pulmonary and hepatotoxicity.

# Quinoxaline derivatives

**Dioxidine** and **quinoxidine**, currently available agents in this class, are used for the treatment of hard formes of anaerobic and mixed aerobic-anaerobic infection.

*Usage*

- These agents have extended spectrum of action which includes Pseudomonas aeruginosa, Proteus vulgaris, pathogenic anaerobes. They are effective in the case of resistance of micro-organisms to other antimicrobial drugs. They are used for the treatment of severe purulent inflammatory diseases only at the hospitalized patients because these drugs have high toxicity.

*Adverse effects*

- Dispeptic disorders, headache, skin allergic reactions

# Oxazolidinones

- **Oxazolidinones** are used as synthetic antimicrobial agents. Some of the most important oxazolidinones are used against gram-positive pathogens, including superbugs such as *Methicillin-resistant Staphylococcus aureus*.

- Developed during the nineties when several bacterial strains were becoming resistant against such antibiotics as vancomycin. These antibiotics are considered as a choice of last resort where every other antibiotic therapy has failed.

- **Linezolid** (Zyvox), the only currently available agent in this class, is available for intravenous administration and also has the advantage of having excellent oral bioavailability.

# Linezolid (Zyvox or Zyvoxid)

*Usage*

- It is usually reserved for the treatment of serious bacterial infections where older antibiotics have failed due to antibiotic resistance. Conditions such as skin infections or nosocomial pneumonia where methicillin or penicillin resistance is found are indicators for linezolid use.
- Linezolid is effective against gram-positive pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes)*. It has almost no effect on gram-negative bacteria and is only bacteriostatic against most *Enterococcus species*. Linezolid also provides some anaerobic coverage.

*Mechanism of Action*

- Linezolid works on the initiation of protein synthesis. It does this by stopping the 30S and 50S subunits of the ribosome from binding together. Linezolid binds on the 23S portion of the 50S subunit close to the peptidyl transferase and chloramphenicol binding sites. This then stops the interaction with the 30S subunit.

*Adverse effects*

- Side effects include rashes, loss of appetite, diarrhea, nausea, constipation and fever. A small number of patients will incur a severe allergic reaction, or tinnitus, or pseudomembranous colitis.